PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 April 2000 (18.04.00)	
International application No. PCT/GB99/02729	**Applicant's or agent's file reference** REP05827WO
International filing date (day/month/year) 20 August 1999 (20.08.99)	**Priority date** (day/month/year) 28 August 1998 (28.08.98)
Applicant HARRISON, Peter, John	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 March 2000 (23.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

15

PATENT COOPERATION TREATY

RECD 10 OCT 2000
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
REP05827WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/02729	20/08/1999	28/08/1998
International Patent Classification (IPC) or national classification and IPC C07K16/00		
Applicant KS BIOMEDIX LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/03/2000	06.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mennessier, T Telephone No. +49 89 2399 8687

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02729

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-7	as originally filed	

Claims, No.:

1-7,8 (part)	as originally filed	
8 (part),9,10	with telefax of	31/08/2000

Drawings, sheets:

1/1	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-7 (as a whole) and 8-10 (part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 8-10 (part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-7.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	8-10
Industrial applicability (IA)	Yes:	Claims	8-10
	No:	Claims	

2. Citations and explanations

see separate sheet

1. Preliminary remarks

Reference is made to the following documents which were cited in the international search report:

D1: *Hybridoma*, 18(2), 1999 April, 183-91
D2: WO 92/01059

D1 is an intermediate document to which the inventor appears to have contributed. Document D1 may be regarded at least with respect to some aspects as a non-patent literature counterpart of the present application.

2. Comments with respect to item I

The sequence listing as originally filed (four pages numbered from 1 to 4) is also part of the application documents taken into consideration for the present examination.

3. Comments with respect to item III

Due to the back-reference to claim 1 newly introduced thereinto claim 8 suffers from the severe lack of clarity identified in the international search report (see the sheet entitled "*Further information continued from PCT/ISA 210*") with respect to claim 1 which has hindered the ISA from carrying out a meaningful search into the state of the art on the basis of this latter claim.

4. Comments with respect to item V

a) Preliminary remark

In view of the above comments claims 8-10 have been examined only for that part of their subject-matter which corresponds to the said claims as originally filed.

b) Novelty

An antibody as defined in claim 8, a polynucleotide molecule encoding the same (see claim 9) and a cloning vehicle comprising such a polynucleotide (see claim 10) appear not to be disclosed in the relevant state of the art (see the non-intermediate documents cited in the international search report). Therefore, the subject-matter of claims 8-10 can be regarded as new, in accordance with the requirements of Article 33(2) PCT.

c) Inventive step

Whereas it has been evidenced in the experimental part that the single-chain Fv antibody referred to therein as "6H9" which represents an antibody as defined in claim 8 is more acido-resistant than two other anti-CEA antibodies, namely the A5B7 antibody (which is described in document D2) and the MFE single-chain Fv (which the IPEA could not identify among the known anti-CEA antibodies), it has not been established that the said 6H9 has an affinity for CEA at a pH corresponding to a clinical use (tumor targeting or imaging) being significantly different from that of the said A5B7 and scFv MFE antibodies. More particularly, there is no demonstration or suggestion that oral administration (assumed to be faced with acid pH conditions) of the claimed antibodies would be efficient in the treatment of any particular disease, and, if so, would furthermore be more efficient than oral administration of any known antibody such as the A5B7 antibody in the treatment of the same disease. Therefore, it cannot be considered that the feature "*acido-resistant*" provide the claimed antibodies with any unexpected and unambiguous advantage over the antibodies of the state of the art.

Hence, it has to be concluded that, contrary to the requirements of Article 33(3) PCT, the subject-matter of claim 8 does not involve an inventive step, the same conclusion applying *de facto* to the subject-matter of each of claim 9 and claim 10.

d) Intermediate document

Should the various aspects of the invention as defined in claims 8-10 appear not to be entitled to the claimed priority date, document D1 should be taken into consideration when examining whether it is new and/or involves an inventive step.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02729

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/00 C07K16/30 C12N15/13 C12N15/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JACKSON, H. ET AL: "Antigen specificity and tumor targeting efficiency of a human carcinoembryonic antigen-specific scFv and affinity -matured derivatives" BR. J. CANCER (1998), 78(2), 181-188 , XP002128798 page 181 -page 182 page 182; table 1 --- -/--	8-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2000	11 02.00
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Mennessier, T

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PIETERSZ G A ET AL: "Preclinical characterization and in vivo imaging studies of an engineered recombinant technetium-99m-labeled metallothionein-containing anti-carcinoembryonic antigen single-chain antibody." JOURNAL OF NUCLEAR MEDICINE, (1998 JAN) 39 (1) 47-56. , XP002128799 page 47 -page 51 page 51; table 1 ---	8-10
A	OSBOURN, JANE K. ET AL: "Generation of a panel of related human scFv antibodies with hig affinities for human CEA" IMMUNOTECHNOLOGY (1996), 2(3), 181-196 , XP000645453 page 181 -page 184 page 190; table 2 ---	8-10
A	BEGENT, R. H. J. ET AL: "Clinical evidence of efficient tumor targeting based on single - chain Fv antibody selected from a combinatorial library" NAT. MED. (N. Y.) (1996), 2(9), 979-984 , XP002128877 the whole document ---	8-10
A	WO 91 01990 A (HOPE CITY) 21 February 1991 (1991-02-21) page 3 page 17 ---	8-10
A	WO 92 01059 A (CELLTECH LTD) 23 January 1992 (1992-01-23) page 5-13 page 16-30 ---	8-10
P,X	OSBORNE J ET AL: "Novel super-high affinity sheep monoclonal antibodies against CEA bind colon and lung adenocarcinoma." HYBRIDOMA, (1999 APR) 18 (2) 183-91. , XP002128800 the whole document -----	8-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9101990 A	21-02-1991	US 5081235 A	14-01-1992
		AU 629401 B	01-10-1992
		AU 6344790 A	11-03-1991
		CA 2035899 A	27-01-1991
		DE 69018801 D	24-05-1995
		DE 69018801 T	19-10-1995
		EP 0436016 A	10-07-1991
		JP 2966924 B	25-10-1999
		JP 4502258 T	23-04-1992
		US 5075431 A	24-12-1991
WO 9201059 A	23-01-1992	AT 137534 T	15-05-1996
		AU 651984 B	11-08-1994
		AU 8200591 A	04-02-1992
		CA 2065325 A	06-01-1992
		DE 69119211 D	05-06-1996
		DE 69119211 T	19-12-1996
		EP 0491031 A	24-06-1992
		GB 2251859 A,B	22-07-1992
		GB 2276169 A	21-09-1994
		JP 5502587 T	13-05-1993
		US 5877293 A	02-03-1999

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7

Whereas the invention as defined in claims 1-7 relates to "high-affinity" monoclonal antibodies, it is not clear what is meant under the term "high-affinity" which determines an essential technical feature of the invention. In this respect, it has to be noted that the affinity of the claimed antibodies has not been quantified in the description by measuring the affinity constant in accordance with the common practice, i.e., in such a way that a significant comparison with the monoclonal antibodies of the relevant state of the art could have been made. Therefore, it has not been possible to carry out a meaningful search into the state of the art.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/GB 99/02729

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.